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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Chiaki Hidai

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EXAMINER

HADDAD, MAHER M

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/563,166	Applicant(s) HIDAI, CHIAKI	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 3-13 and 17-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 14-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/27/06</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Claims 1-27 are pending.
2. Applicant's election with traverse of Group I, claims 1-3 and 14-16 drawn to a protein, a reagent, a fusion protein or a drug comprising SEQ ID NOs: 6, 8, 10, 12, 14, 18 and 24, and SEQ ID NO: 24 as the species, filed on 3/28/08, is acknowledged.

Applicant's traversal is on the grounds that he disagrees and reserves the right to address the Patent 6,812,339 teachings in an office action on the merits. This is not found persuasive because Applicant did not point to the supposed error in the restriction requirement. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

3. Claims 3 (non-elected species), 4-13 and 17-27 (non-elected Groups) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-2 and 14-16 are under examination as they read on a protein, a reagent, a fusion protein or a drug comprising SEQ ID NOs: 6, 8, 10, 12, 14, 18 and 24, and SEQ ID NO: 24 as the species.

5. Claims 14-15 are objected to because it depends on non-elected claim 3.

6. Applicant's IDS, filed 10/27/06, is acknowledged.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide consisting of SEQ ID NOs: 6 (4-1(1-348)), 8 (4-15, (1-365)), 10 (4-14, (1-368)), 12 (4-13, (1-388)), 18 (mXY, (123-348)) or 24 (hXY, (123-348)) which has deposition activity onto extracellular matrix, or fusion protein comprising a polypeptide consisting of SEQ ID NOs: 6, 8, 10, 12, 18 or 24 linked to a molecule of interest to be expressed, does not reasonably provide enablement for a protein "comprising" the amino acid sequence as shown in SEQ ID NO: 18 or 24 in claims 1-2(a), a protein which "comprises" the amino acid sequence as shown in SEQ ID NO: 18 or 24 "having deletion, substitution or addition of one or several amino acids" and has deposition activity onto extracellular matrix in claims 1-2(b) or a reagent for identifying a site of deposition in extracellular matrix "comprising" the protein according to claim 1 or 2 in claim 14, or a fusion protein "composed" of the protein according to claim 1 or 2 linked to a molecule of interest to be expressed in claim 15 or "a drug delivery system" "comprising" the fusion protein in claim 16. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses that the object of the invention is to provide a partial fragment of Del-1 comprising a region capable of efficiently adhering onto extracellular matrix. The specification further discloses that extensive and intensive researches toward the solution of the above problem leads to the regions neighboring the discoidin-I-like domains efficiently deposit onto extracellular matrix (see page 2, lines 1-5). Table 1 on page 10 and Fig. 1 provides summarized the regions contained in the Del-1 partial fragments and the results of measurement of deposition activities of individual fragments using alkaline phosphatase activity. Example 2, on page 21 of the specification discloses the deposition activity of Del-1 partial fragments onto extracellular matrix. the specification on page 21, lines 23-26 discloses that XY and human XY have higher alkaline phosphatase activity than the wild-type full-length Del-1, and CB and CY have some alkaline phosphatase activity. On the other hand, no alkaline phosphatase activity was recognized in XC and YB. The specification discloses that it was believed that the active center region is CY (218-248 of SEQ ID O: 2) (see page 21, lines 26-29). The specification further discloses that the ligation of CY and XC which results in XY has deposition activity about 10 times higher than that of CY (active center region) alone. XC alone has little deposition activity. Therefore, it was believed that XC is a positive regulation region for deposition activity which improves deposition activity onto extracellular matrix (see page 21, lines 30-34).

At issue the protein that comprising SEQ ID NO:24, the term "comprising" is open-ended, it would open up the claimed sequence to include additional unspecified amino acids on either or both sides of the N-terminal or C-terminal of the sequence SEQ ID NO: 24 even in large amounts. See MPEP 2111.03. Such amino acids would significantly interfere with the activity of the peptide. There is insufficient guidance as to which amino acids outside SEQ ID NO: 24 would maintain the capability to of efficiently adhere onto extracellular matrix. It would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have the same functional activity. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed peptides. Without sufficient guidance, the changes which can be made in the structure of "SEQ ID NO:24" and still provide efficient deposit onto extracellular matrix is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. A center region (CY) and positive regulation region (XC) of Del-1 (collectively claimed SEQ ID NO: 24) linked to several negative regulation region (YB) on either or both sides of the N-terminal or C-

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terminal would not be expected to provide deposition activity onto extracellular matrix.

Further, at issue the recitation that the claimed protein having “deletion, substitution or addition of one or several amino acids” in claim 1b and 2b. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single “lysine” residue at position 118 of acidic fibroblast growth factor by “glutamic acid” led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Wang et al. (JBC 276:49213-49220), who show that a single amino acid determines lysophospholipid specificity of the S1P1 (EDG1) and LPA1 (EDG2) phospholipids growth factor receptors (e.g., abstract). Wang et al shows that a single amino acid Glu¹²¹ in S1P1/EDG1, which corresponds to Gln¹²⁵ in LPA1/EDG2, influences the specificity for S1P or LAP (see page 49213 last ¶). Mutating the Arg-Glu-Gly motif to that is conserved among LPA receptors Arg-Gln-Gly, lead to ligand selectivity switch in concert with the mutations. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the polypeptide to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Moreover, the “drug delivery system”, DDS, of claim 16 is at issue. The specification on page 19, under Section 8) discloses that an example of DDS such as a gene encoding a fusion protein composed of fragment 4-1 comprising the center region and the positive regulation region and an enzyme that converts a precursor of an anticancer agent into the anticancer agent is transferred into cancer tissues in advance. Subsequently, a large dose of the precursor is administered. Then, a higher drug concentration is achieved in cancer tissues than normal tissues. After the treatment, by introducing a gene encoding fragment CB (SEQ ID NOS: 13 and 14) comprising the negative regulation region, the gene product of the previously introduced gene is released into blood and becomes capable of removal by hemodialysis or the like. However, in view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective DDS therapies using claimed SEQ ID NO: 24, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the intended use of the claimed product and absent working examples providing evidence which is reasonably predictive that the claimed DDS are effective for *in vivo* use.

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Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-2 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a polypeptide consisting of SEQ ID NOs: 6 (4-1(1-348)), 8 (4-15, (1-365)), 10 (4-14, (1-368)), 12 (4-13, (1-388)), 18 (mXY, (123-348)) or 24 (hXY, (123-348)) which has deposition activity onto extracellular matrix, or fusion protein comprising a polypeptide consisting of SEQ ID NOs: 6, 8, 10, 12, 18 or 24.

Applicant is not in possession of a protein "comprising" the amino acid sequence as shown in SEQ ID NO: 18 or 24 in claims 1-2(a), a protein which "comprises" the amino acid sequence as shown in SEQ ID NO: 18 or 24 "having deletion, substitution or addition of one or several amino acids" and has deposition activity onto extracellular matrix in claims 1-2(b) or a reagent for identifying a site of deposition in extracellular matrix "comprising" the protein according to claim 1 or 2 in claim 14, or a fusion protein "composed" of the protein according to claim 1 or 2 linked to a molecule of interest to be expressed in claim 15 or "a drug delivery system" "comprising" the fusion protein in claim 16.

The Examiner draws Applicant's attention to the recent Written Description Training Materials published April 11, 2008. Specifically Example 10, claim 3.

Applicant has disclosed only partial Del-1 fragments acid of SEQ ID NO: 6, 8, 10, 12, 18 or 24; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112,

¶1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the

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genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2000, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 1-2 and 14-16 are rejected under 35 U.S.C. 102(e) as being anticipated by US patent 6,812,339 (of record) as is evidence by the specification on Fig. 1.

The '339 patent teaches a 448 amino acid protein (patented SEQ ID NO: 10130) which comprises the amino acid sequence of SEQ ID NO: 24 at positions 91-316 (see patented SEQ ID NO: 10130 in particular). While the prior art teachings may be silent as to the “deposition activity onto extracellular matrix” per se; the products in the reference are the same as the claimed product. Therefore “deposition activity onto extracellular matrix” is considered inherent properties. As is evidenced by the specification on Table 1 that all the polypeptide containing XY region (claimed SEQ ID NO: 24) are positive for deposition into the ECM/Medium (see Del-1 major (full length), 4-8, 4-13, 4-14, 4-1 fragments). The patent teaches variant proteins of the present invention can be attached to heterologous sequences to form chimeric or fusion proteins and a composition comprising the protein. A fusion protein can be provided which adds a domain that

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allows the protein to be bound to a matrix. For example, glutathione-S-transferase/I125 fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, Mo.) or glutathione derivatized microtitre plates, which are then combined with the cell lysates (e.g., .sup.35 S-labeled) and a candidate compound, such as a drug candidate, and the mixture incubated under conditions conducive to complex formation.

The reference anticipates that claimed invention.

12. Claims 1-2 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by US patent 5,874,562 (IDS reference A01).

The '562 patent teaches a 513 amino acid protein comprising claimed SEQ ID NO: 24, at positions 155-381 (see patented SEQ ID NO: 14) have two substitutions (P92K and S123F) and a single addition (R between aa 92 and 93). Further, the patent claims a polypeptide (460 amino acids) comprising the amino acid sequence as shown in patented SEQ ID NO:14 from residue #54 through #513 (see patented claims 21-27), which comprises SEQ ID NO:24, with the substitution and addition above. The 5874562 patent further teaches a 321 amino acid protein comprising SEQ ID NO: 24 having deletion of several amino acids (lacking the N-terminal 35aa of claimed SEQ ID NO: 24), substitution (see below), and addition of several amino acids 193-321. See patented SEQ ID NO: 21 and Fig. 7. The patent further teaches that a del-1 or a modified del-1 sequence may be ligated to a heterologous sequence to encode a fusion protein. For example, for screening of peptide libraries for molecules that bind Del-1, it may be useful to encode a chimeric Del-1 protein expressing a heterologous epitope that is recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between a Del-1 sequence and the heterologous protein sequence, so that the Del-1 may be cleaved away from the heterologous moiety (see col., 10 bridging ¶ to col., 11). The patent further teaches expression vectors derived from viruses such as retroviruses, vaccinia virus, adeno-associated virus, herpes viruses, or bovine papilloma virus, may be used for delivery of recombinant Del-1 into the targeted cell population (DDS) (see Section 5.6.2. THERAPEUTIC USES OF A DEL-1 POLYNUCLEOTIDE). The claimed functional property "has deposition activity onto extracellular matrix" is inherent.

Qy 36 CSGPLGIEGGIISNQQTASSTHRALFGLQKWYPYARLNKKGLINAWTAAENDRW_PWI 94

|||||

Db 1 CSGPLGIEGGIISNQQTASSTHRALFGLQKWYPYARLNKKGLINAWTAAENDRWNRWI 60

Qy 95 QINLQRKMRVTGVITQGAKRIGSPEYIKSYKIAYSNDGKTWAMYKVKGTDNEDMVFRGNID 154

|||||

Db 61 QINLQRKMRVTGVITQGAKRIGSPEYIKYKIAYSNDGKTWAMYKVKGTDNEDMVFRGNID 120

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Qy 155 NNTPYANSFTPIKAQYVRLYPQVCRRHCTLRMELLGCELSGCSEPLGMKSGHIQDYQIT 214



Db 121 NNTPYANSFTPIKAQYVRLYPQVCRRHCTLRMELLGCELSGCSEPLGMKSGHIQDYQIT 180

Qy 215 ASSIFRTLNMDM 226



Db 181 ASSIFRTLNMDM 192

The reference teachings anticipate the claimed invention.

13. Claims 1-2 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by US patent 5/887,281 (IDS reference A02).

The '281 patent claims a polypeptide comprising three epidermal growth factor-like domains and two discoidin I/factor VIII-like domains contained within the amino acid sequence as shown in patented SEQ ID NO:14 (see patented claims 39, 40, 49-50, 52-53) comprising claimed SEQ ID NO: 24 (at positions 155-381) with two substitution (P92K and S123F) and a single addition (R between positions 92 and 93) of SEQ ID NO: 24. . The '281 patent further teaches a 321 amino acid protein comprising SEQ ID NO: 24 having deletion of several amino acids (lacking the N-terminal 35aa of claimed SEQ ID NO: 24), substitution, and addition of several amino acids 193-321. See patented SEQ ID NO: 21 and Fig. 8. The patent further teaches that a del-1 or a modified del-1 sequence may be ligated to a heterologous sequence to encode a fusion protein. For example, for screening of peptide libraries for molecules that bind Del-1, it may be useful to encode a chimeric Del-1 protein expressing a heterologous epitope that is recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between a Del-1 sequence and the heterologous protein sequence, so that the Del-1 may be cleaved away from the heterologous moiety (see col., 10 bridging ¶ to col., 11). The patent further teaches expression vectors derived from viruses such as retroviruses, vaccinia virus, adeno-associated virus, herpes viruses, or bovine papilloma virus, may be used for delivery of recombinant Del-1 into the targeted cell population (DDS) (see Section 5.6.2. THERAPEUTIC USES OF A DEL-1 POLYNUCLEOTIDE). The claimed functional property "has deposition activity onto extracellular matrix" is inherent.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

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15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 11, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644